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ORIGINAL ARTICLE

Kidney transplant outcomes from older deceased donors: a paired kidney analysis by the European Renal Association–European Dialysis and Transplant Association Registry

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SUMMARY

As the median age of deceased kidney donors rises, updated knowledge of transplant outcomes from older deceased donors in differing donor–recipient age groups is required. Using ERA-EDTA Registry data we determined survival outcomes of kidney allografts donated from the same older deceased donor (55–70 years), and transplanted into one recipient younger and one recipient of similar age to the donor. The recipient pairs were divided into two groups: group 1; younger (median age: 52 years) and older (60 years) and group 2; younger (41 years) and older (60 years). A total of 1410 adults were transplanted during 2000–2007. Compared to the older recipients, the mean number of functioning graft years at 10 years was 6 months longer in the group 1 and group 2 younger recipients ($P < 0.001$). Ten-year graft survival was 54% and 40% for the group 1 younger and older recipients, and 60% and 49% for the group 2 younger and older recipients. Paired Cox regression analyses showed a lower risk of graft failure (group 1 younger; adjusted relative risk [RRa]:0.57, 95% CI:0.41–0.79, and group 2 younger; RRa:0.63, 95% CI:0.47–0.85) in younger recipients. Outcomes from older deceased donor allografts transplanted into differing donor–recipient age groups are better than previously reported. These allografts remain a valuable transplant resource, particularly for similar-aged recipients.

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Key words
deceased donors, donor age, graft survival, kidney transplant, registry

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Introduction

Global variations exist in the criteria for deceased donor kidney allocation [1]. Some European deceased donor kidney allocation schemes such as that of the UK, Spain, France and Scandiatransplant take into consideration the age difference between the donor and the potential recipient, whereas others such as Eurotransplant do not (for patients aged <65 years) [1]. Deceased donor kidney allocation algorithms that are designed to account for the age difference between the donor and the potential recipient, will where possible allocate younger kidneys to younger patients and older kidneys to older patients [2]. However, the definition of an acceptable donor–recipient age difference also varies between allocation schemes, for example in Italy, a difference between the donor and recipient ages of less than 15 years is preferred, whereas in Spain, a difference of less than 10 years is preferred. Whilst allocation schemes may take the donor–recipient age difference into account, older donor kidneys are still being allocated to patients of various ages.

The rationale of age matching is twofold; firstly by matching the potential lifespan of the allograft with the recipient, the organ is used efficiently. Secondly, young recipients receiving old deceased donor kidneys have been shown to have worse graft survival outcomes including higher rates of graft failure from rejection compared with young recipients receiving young deceased donor kidneys [3–6]. However, many of these previous studies were performed in the 1990s and early 2000s when the median age of both the donors and recipients was lower, and graft survival outcomes were worse.

Over the past two decades, the demand for transplantable organs has resulted in an increased utilization of older 'marginal' deceased donor kidneys. Subsequently, the median age of deceased kidney donors has steadily increased [7, 8]. Within Northern Europe, the median age of deceased kidney donors has risen from approximately 35 years in the 1990s to approximately 55 years in 2015 [9, 10]. As the median age of deceased kidney donors and their recipients is now approximately 55 years old, and transplant outcomes over the past two decades have improved [11], updated patient and allograft survival outcomes of kidneys transplanted from deceased donors aged 55 years and over (i.e. above the median deceased donor age) into recipients of differing ages are required.

Using renal registry and transplant registry data from nine European countries/regions, the aim of this study was to quantify how long kidney allografts from older deceased donors are expected to function for whilst considering the donor–recipient age difference. Using a paired analysis study design, we analysed patient and allograft survival outcomes of two kidney allografts donated from the *same* deceased donor aged between 55 and 70 years, and transplanted into two recipients of differing ages; a recipient younger than the donor and a recipient of similar age to the donor. This method ensures that a kidney from the same donor is present in both groups, thereby eliminating from the analyses the effects of the donor factors on patient and graft outcomes. Furthermore, we used a novel technique within the kidney transplantation literature, the restricted mean survival time, to quantify the mean difference in the graft survival time between the groups [12].

Materials and methods

Data collection and study groups

Renal and transplant registries within nine European countries or regions supplying data to the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry were asked to

identify transplant recipients fulfilling the specified inclusion criteria. Where necessary additional data required for the survival analyses were obtained from the ERA-EDTA Registry database using a unique anonymized patient identifier (see Table 1 for data sources).

The study cohort consisted of all patients aged 18 years and over who received their first kidney only transplant between 2000 and 2007 from a deceased donor aged between 55 and 70 years. As the median deceased donor age in many European countries is 55 years, the age range 55–70 was specifically chosen to reflect donors just above the average age of deceased donation. Only cases where *both* kidneys from the *same* deceased donor were transplanted into recipients of differing ages were considered. One transplant recipient had to be within 5 years of the donor's age (as these recipients had a median age at transplantation above the current median transplant age we called these recipients the older recipients), and the second transplant recipient from the same deceased donor had to be at least 6 years or more younger than the donor. Given the large range of the donor–recipient age gradient, that is the difference in years between the donor and recipient ages, we subdivided the recipient pairs into two groups; termed group 1 and group 2. The cut-off point for the two groups was determined pre-analysis using univariate Cox regression with restricted cubic regression splines analysis [13]. The groups were those ≥6 to <13 years younger than the donor and their paired older recipients (group 1) and those ≥13 years younger than the donor and their paired older recipients (group 2). The chi-squared test and Mann–Whitney *U*-test were used to compare the group characteristics.

Statistical analyses

Table 2 provides an overview of the different survival analyses used in this article, that is the survival outcome investigated and analysis method used, the starting point, the event(s) of interest, competing event(s), censoring observations and the potential confounders accounted for in the multivariable analysis. In all of the survival analyses, the date of kidney transplantation was taken as the starting point of the analysis, and patients were followed until the event of interest, a censored observation and/or a competing event (see Table 2 for details) or the end of the follow-up period (31 December 2013).

Restricted mean number of functioning graft years

The restricted mean survival is a way in which one quantifies the mean survival of a treatment group measured up to a specific time point. It is computed as the total area under the covariate-adjusted graft survival curve up to a specific time point. By comparing the mean survival of two groups, one obtains an assessment of a treatment effect over a time interval [12]. This method has the advantages of being relatively easy to understand and can be used even in the presence of nonproportional hazards [14]. We estimated the restricted mean survival time of functioning graft years (i.e. the number of years the allograft was functional before loss secondary to graft failure or death with a functioning graft). We repeated this process four times with increasing follow-up times thereby obtaining the mean graft survival time restricted to one, five, seven

Table 1. Additional data sources and number of recipients provided by country or region.

Country/Region supplying data	Data source(s)	Number of recipients	Proportion (%)
Austria	Austrian dialysis and transplant registry	90	6.4
Basque country (Spain)	Information unit about renal patients from the Basque Country	58	4.1
Catalonia (Spain)	Catalan Renal Registry, Catalan Transplant Organization, Health Department, Generalitat of Catalonia	182	12.9
Denmark	Danish Renal Registry and Scandiatransplant	46	3.3
Finland	Finnish Registry for Kidney Diseases and the Finnish Kidney Transplant Registry	96	6.8
the Netherlands	Dutch transplant foundation	138	9.8
Norway	Norwegian Renal Registry	38	2.7
Sweden	Swedish Renal Registry and Scandiatransplant	96	6.8
United Kingdom	United Kingdom Renal Registry and UK Transplant Registry held by NHS Blood and Transplant	666	47.2
Total		1410	100

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and 10 years of follow-up [12] (i.e. what was the average time the older donor kidneys were functional for in one-, five-, seven- and 10-year follow-up). We adjusted for important transplant-related parameters selected a priori which could influence the functioning of the graft, that is cold ischaemia time and human leucocyte antigen (HLA) mismatch (favourable HLA-A, HLA-B and HLA-DR mismatches: 000, 100, 010, 110 versus all other mismatches). The SAS macro %RESMEAN was used for this analysis [12].

Cumulative risk of graft failure

The cumulative incidence competing risk method was used to estimate the unadjusted 10-year cumulative risk of graft failure and death [15].

Relative risk of allograft failure and patient mortality between younger and older recipients

Cox regression was used to estimate the relative risk of graft failure (defined as graft loss from all causes or death with a functioning graft) [16] and the relative all-cause mortality risk between the older recipient group and the corresponding younger recipient group. Furthermore, Cox regression analysis was used to estimate the relative risk of graft failure in which the competing event of death was interpreted as a censored event [15] (henceforth termed death-censored graft failure). All Cox regression analyses were stratified by the donor pair, whereby the patient or kidney allograft outcome of the older recipient was directly compared to the patient or kidney allograft outcome of the younger recipient from the same older deceased donor. This removed any donor-associated factors from the analysis. Adjustments were made in a stepwise manner. Firstly, we only adjusted for transplant-related parameters which could influence graft survival, that is cold ischaemia time and HLA mismatch. Secondly, we added recipient factors which could influence graft survival, that is, recipient sex, primary renal disease and initial modality of renal replacement therapy.

A two-tailed *P*-value of less than 0.05 was considered statistically significant. Analyses were performed using SAS version 9.3 and R version 3.0.2.

Results

Baseline characteristics

In total 1410 paired kidney transplant recipients from 705 deceased donors aged between 55 and 70 years were included in the study (Table 3). The recipients in group 1 consisted of the younger recipients which were within ≥6 to <13 years of the donor's age ($N = 336$), termed group 1 younger recipients and their corresponding paired older recipients which were within 5 years of the same deceased donor's age ($N = 336$), termed group 1 older recipients; and the recipients in group 2 consisted of the younger recipients which were ≥13 years younger than the donor ($N = 369$), termed group 2 younger recipients and their corresponding paired older recipients which were within 5 years of the same donor's age ($N = 369$), termed group 2 older recipients.

Table 3 shows the baseline characteristics of the recipient groups and the corresponding donor details. The median donor–recipient age gradient was 8.1 years (interquartile range [IQR] 7.0–10.0) for the group 1 younger recipients and 20 years (IQR 16.0 to 25.5) for the group 2 younger recipients, whereas both groups of paired older recipients were 0.9 years (IQR −2.0 to 3.0) younger than the donor. The median age at kidney transplantation was 52.0 years (IQR 49.0 to 56.3) for the group 1 younger recipients and 40.7 years (IQR 34.0 to 45.0) for the group 2 younger recipients. The median age of the older recipients in both groups was 60.0 years (IQR 57.0 to 64.0). At the time of donation, the deceased donors donating to group 1 had a median age of 61.0 years (IQR 58.0 to 65.0), and the deceased donors donating to group 2 had a median age of 60.0 years (IQR 57.0 to 63.0).

Restricted mean number of functioning graft years

Table 4 shows the restricted mean number of functioning graft years, that is the number of years, the allograft was functional before loss secondary to graft failure or death with a functioning graft. Restricted to 1 year of follow-up, there was no difference in the mean number of functioning graft years between the younger and older recipients in group 1 and the younger and older recipients in group 2. The difference in the mean number of functioning graft years between the younger and older recipients in both groups increased with the duration of follow-up. By 10-year follow-up, the difference in the mean number of functioning graft years was 0.45 (95% confidence interval [CI]: 0.18 to 0.72, i.e. 5.4 months) and 0.52 (95% CI: 0.27 to 0.77, i.e. 6.2 months longer) years longer in the group 1 younger and group 2 younger recipients, respectively, compared to their paired older recipients ($P < 0.001$).

Table 2. Overview of the different types of survival analyses used in this article. The adjustments were made in a stepwise manner; (1) transplant-related parameters influencing graft survival, that is cold ischaemia time (CIT) and human leucocyte antigen mismatch (HLA MM) and (2) recipient factors influencing graft survival, that is recipient sex, primary renal disease and initial modality of renal replacement therapy.

Survival analysis outcome	Survival analysis method	Starting point	Event of interest	Competing event	Censoring observations	Variables adjusted for
Cumulative risk of graft failure	Cumulative incidence competing risk method	Date of kidney transplant	Graft failure	Death with a functioning graft*	End of follow-up period Loss to follow-up	
Restricted mean number of functioning graft years	Area under the estimated graft survival function	Date of kidney transplant	Graft failure or Death with a functioning graft		End of follow-up period or End of 10-year follow-up; whichever event occurred first Loss to follow-up	CIT, HLA MM
Relative risk of death-censored graft failure between paired recipients	Pair-stratified Cox regression (cause-specific model)	Date of kidney transplant	Graft failure		Death with a functioning graft† End of follow-up period Loss to follow-up	1. CIT & HLA MM. 2. CIT, HLA MM, recipient sex, PRD & first RRT modality
Relative risk of graft failure between paired recipients	Pair-stratified Cox regression	Date of kidney transplant	Graft failure or Death with a functioning graft		End of follow-up period Loss to follow-up	1. CIT & HLA MM. 2. CIT, HLA MM, recipient sex, PRD & first RRT modality
Relative risk of mortality between paired recipients	Pair-stratified Cox regression	Date of kidney transplant	Patient death		End of follow-up period Loss to follow-up	1. CIT & HLA MM. 2. CIT, HLA MM, recipient sex, PRD & first RRT modality

HLA MM, human leucocyte antigen mismatch; CIT, cold ischaemia time; PRD, primary renal disease; RRT, renal replacement therapy. End of follow-up period: 31 December 2013.

*Using the cumulative incidence competing risk method, 'death with a functioning graft' was interpreted as a competing event.

†Using the pair-stratified cause-specific Cox regression, 'death with a functioning graft' was interpreted as a censored event [15].

Table 3. Baseline characteristics of the group 1 and group 2 younger recipients and their paired older recipients and the corresponding donor details. (RRT: renal replacement therapy. HLA: human leucocyte antigen mismatch [favourable HLA-A, HLA-B and HLA-DR mismatches: 000, 100, 010, 110]. IQR: interquartile range).

	Group 1			Group 2			
	Younger recipients, (≥6 to <13 years younger)	Older recipients	*P*-value	Younger recipients, (≥13 years younger)	Older recipients	*P*-value	Missing data (%) all groups
Number	336	336		369	369		
Recipient sex (% male)	63.4	64.3	0.81	63.1	68.0	0.16	0
Age at transplantation, years (median, IQR)	52.0 (49.0, 56.3)	60.6 (57.0, 64.0)	<0.01	40.7 (34.0, 45.0)	60.0 (56.7, 63.6)	<0.01	0
Pretransplant dialysis time, years (median, IQR)	2.1 (1.1, 3.9)	2.5 (1.3, 4.0)	0.51	2.4 (1.2, 4.2)	2.5 (1.4, 4.1)	0.78	0
First RRT modality (%);			0.22			0.29	0.1
Haemodialysis	66.4	69.1		58.3	59.6		
Peritoneal dialysis	28.0	28.0		35.5	30.9		
Preemptive transplant	5.7	3.0		6.0	9.2		
Primary renal disease (%);			0.25			0.02	Unknown = 16.7%
Diabetes mellitus	14.3	15.5		10.3	9.5		
Hypertension/renovascular	9.2	10.4		6.8	9.2		
Glomerulonephritis/sclerosis	19.4	24.4		27.9	19.0		
Other (including unknown)	57.1	49.7		55.0	62.3		
Donor age, years (median, IQR)	61.0 (58.0, 65.0)	61.0 (58.0, 65.0)	NA	60.0 (57.0, 63.0)	60.0 (57.0, 63.0)	NA	0
Donor–recipient age gradient, years (median, IQR)	8.1 (7.0, 10.0)	0.9 (-2.0, 3.0)	<0.01	20.0 (16.0, 25.5)	0.9 (-2.0, 3.0)	<0.01	0
Donor type (%);			NA			NA	0
Donation after brain death	89.6	89.6		90.5	90.5		
Donation after cardiac death	10.4	10.4		9.5	9.5		
Cold ischaemia time, hrs (median, IQR)	18.4 (15.0, 23.0)	18.0 (15.2, 21.9)	0.49	20.0 (16.0, 25.5)	19.0 (15.7, 23.3)	0.18	14.0
HLA mismatch (% favourable HLA-A, -B, -DR mismatches)	30.1	27.4	0.44	40.1	36.3	0.29	0
Median follow-up time, years (IQR)	7.9 (5.3, 10.3)	7.2 (3.7, 9.9)	0.11	7.4 (4.5, 9.6)	6.9 (3.9, 9.1)	0.47	
Total follow-up time, years	2228.20	2092.23		2571.47	2372.33		

Cumulative risk of graft failure

Figure 1 shows the 10-year cumulative risk of graft failure from all causes, that is graft failure and death with a functioning graft for group 1 (upper panel) and group 2 (lower panel). The 10-year cumulative risk of graft failure from all causes was 46% and 60% for the group 1 younger and older recipients, respectively, and 40% and 51% for the group 2 younger and older recipients, respectively.

Risk of allograft failure and patient survival

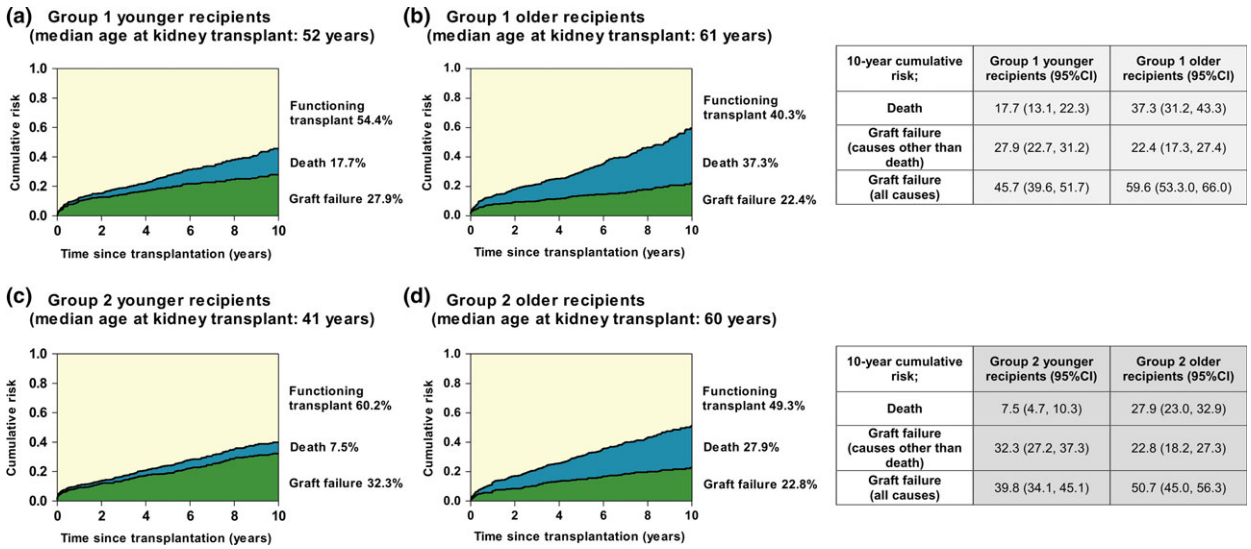
The risk of graft failure (defined as either graft failure or death with a functioning graft) was 43% and 37% lower in the group 1 and group 2 younger recipients, respectively, relative to their paired older recipients (Table 5). However, there was a similar risk of death-censored graft failure in the group 1 and group 2 younger recipient groups compared to their paired older recipients (Table 5). This reflected the fact that the risk of patient death was considerably lower in both younger recipient groups (Table 5).

Discussion

In this study, we have compared the survival outcomes of kidney allografts from older deceased donors whilst considering the donor–recipient age difference. We examined the outcomes of kidney allografts from the same deceased donor aged between 55 and 70 years (median age of 60 years) transplanted into younger recipients (group 1 with a median age of 52 years or group 2 with a median age of 41 years) with the outcomes when transplanted into an 'older' recipient (similar age as donor; median age of 60 years). By performing a paired analysis, whereby a donor kidney is present in the younger recipient group and in the corresponding older recipient group, the effects of the donor factors on patient and graft outcomes are essentially eliminated from the analyses. In addition, this study used a method novel in kidney transplantation, whereby graft survival time was derived using the restricted mean survival time. This technique provides easily interpretable and comparable estimates of the number of functioning graft years gained or lost by a treatment over a specified time interval [12, 17]. Using the restricted mean survival time method, we found that by 10 years of follow-up the mean number of functioning graft years was 6 months longer in the younger recipients compared to the corresponding paired older

Table 4. Mean number of functioning graft years (95% confidence interval) for the group 1 and group 2 younger and older recipients, respectively. Adjusted for cold ischaemia time and human leucocyte antigen mismatch. Differences highlighted in bold indicate a significant difference ($P < 0.05$).

	Group 1			Group 2		
	Mean number of functioning graft years for the younger recipients and the paired older recipients			Mean number of functioning graft years for the younger recipients and the paired older recipients		
Follow-up time restricted to:	Younger recipients (95% CI)	Older recipients (95% CI)	Difference (95% CI)	Younger recipients (95% CI)	Older recipients (95% CI)	Difference (95% CI)
1 year	0.92 (0.89, 0.95)	0.91 (0.87, 0.95)	0.02 (−0.03, 0.06)	0.92 (0.89, 0.95)	0.92 (0.89, 0.95)	−0.004 (−0.05, 0.04)
5 years	4.18 (4.08, 4.28)	4.07 (3.96, 4.17)	0.12 (-0.03, 0.26)	4.24 (4.15, 4.33)	4.09 (3.99, 4.19)	**0.15 (0.01, 0.29)**
7 years	5.58 (5.45, 5.71)	5.38 (5.24, 5.52)	**0.20 (0.01, 0.39)**	5.70 (5.58, 5.82)	5.41 (5.23, 5.54)	**0.29 (0.11, 0.47)**
10 years	7.42 (7.24, 7.60)	6.97 (6.77, 7.17)	**0.45 (0.18, 0.72)**	7.63 (7.47, 7.79)	7.11 (6.94, 7.29)	**0.52 (0.27, 0.77)**
	Based on deceased donors with a median age of 61 (interquartile range, 58–65)			Based on deceased donors with a median age of 60 (interquartile range, 57–63)		



10-year cumulative risk;	Group 1 younger recipients (95%CI)	Group 1 older recipients (95%CI)
Death	17.7 (13.1, 22.3)	37.3 (31.2, 43.3)
Graft failure (causes other than death)	27.9 (22.7, 31.2)	22.4 (17.3, 27.4)
Graft failure (all causes)	45.7 (39.6, 51.7)	59.6 (53.3.0, 66.0)

10-year cumulative risk;	Group 2 younger recipients (95%CI)	Group 2 older recipients (95%CI)
Death	7.5 (4.7, 10.3)	27.9 (23.0, 32.9)
Graft failure (causes other than death)	32.3 (27.2, 37.3)	22.8 (18.2, 27.3)
Graft failure (all causes)	39.8 (34.1, 45.1)	50.7 (45.0, 56.3)

Figure 1 Ten-year cumulative risk of graft failure from all causes (i.e. graft failure and death) for the group 1 younger recipients and their paired older recipients (upper panels a & b) and the group 2 younger recipients and their paired older recipients (lower panels c & d).

recipients. We found the 10-year graft survival from old deceased donor kidneys to be 54% and 40% for the group 1 younger and older recipients, respectively, and 60% and 49% for the group 2 younger and older recipients, respectively. This is much higher than the previously reported survival probabilities of 24% at 8 years in recipients aged <55 years of allografts from deceased donors aged ≥55 years [18] and consistent with other studies showing improvements in graft survival within European populations over time [11]. In contrast to prior studies, we found a similar risk of death-censored graft failure between the younger recipients compared to the older recipients of old deceased donor kidneys.

The 10-year survival probabilities of older deceased donor kidneys reported in this study are higher than the previously quoted survival probabilities [4–6, 18]. For example, Lim *et al.* reported that for allografts from donors aged ≥55 years, eight-year cumulative incidence of death-censored graft failure was 22.3% and 16.4% in recipients aged <55 years and ≥55 years, respectively [5]. The majority of the previously quoted survival probabilities arise from studies predominantly published in the early 2000s using transplant data from the 1990s [6]. Survival probabilities from deceased donors overall (i.e. not stratified by donor age) have improved since the 1990s [11]. This probably explains why our survival probabilities from transplants that occurred between 2000 and 2007 are better.

When compared to the current overall European 10-year deceased donor graft survival outcomes, our results are worse. Our 10-year graft survival outcomes from deceased donors aged between 55 and 70 years are approximately 10% lower than the for overall European deceased donor kidney transplant recipients transplanted in the same time period (10-year graft survival probabilities of 71%, 65% and 54%, for a median recipient transplant age of 41, 50 and 60 years, respectively – unpublished data from the European Renal Association–European Dialysis and Transplant Association [ERA-EDTA] Registry). There are several physiological changes in the older deceased donor kidney which may explain in part, the lower graft survival probabilities obtained in comparison with the overall graft survival probabilities for European deceased donor kidney transplant recipients. At the time of transplantation, older deceased donor kidneys have been shown to have a reduced number of nephrons [19] and evidence of age-related pathology [20]. Furthermore, older deceased donor kidneys are not able to mount an adequate repair response following an injury [21]. These features also render older deceased donor kidneys more susceptible to the effects of longer cold ischaemia times [22]. Although these features in part explain the lower graft survival outcomes we obtained in comparison with the overall graft survival outcomes for European deceased donor kidney transplant recipients, active efforts to reduce cold ischaemia times, in addition to other advances in the procurement of organs and in transplant medicine overall may explain why these results are higher than the historical results. Furthermore, in contrast to prior studies, we found a similar risk of death-censored graft failure between younger recipients compared with older recipients of old deceased donor kidneys. The prior studies from the 1990s to 2000s

Table 5. Relative risk (RR) of death-censored graft failure, graft failure and patient mortality for the group 1 and group 2 younger recipient groups as compared to their paired older recipients.

	Group 1 younger recipients compared with paired older recipients			Group 2 younger recipients compared with paired older recipients		
	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)	Adjusted RR† (95% CI)	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)	Adjusted RR† (95% CI)
Death-censored graft failure	1.03 (0.71, 1.49)	0.79 (0.52, 1.19)	0.84 (0.54, 1.30)	1.30 (0.95, 1.79)	1.14 (0.81, 1.62)	1.04 (0.72, 1. 50)
Graft failure	**0.69 (0.53, 0.90)**	**0.60 (0.45, 0.81)**	**0.57 (0.41, 0.79)**	**0.79 (0.61, 1.01)**	**0.67 (0.50, 0.89)**	**0.63 (0.47, 0.85)**
Patient mortality	**0.49 (0.36, 0.66)**	**0.56 (0.43, 0.71)**	**0.37 (0.25, 0.54)**	**0.23 (0.16, 0.34)**	**0.21 (0.14, 0.30)**	**0.21 (0.15, 0.31)**

*Adjusted for cold ischaemia time and human leucocyte antigen (HLA) mismatch.

†Adjusted for cold ischaemia time, HLA mismatch, recipient sex, primary renal disease and initial modality of renal replacement therapy. Differences highlighted in bold indicate a significant difference ($P < 0.05$).

often reported an inferior death-censored graft survival in younger recipients of older donor kidneys [5, 18, 23]. As with the improvements in 10-year graft survival, these new findings may also be explained by developments in transplant medicine such as organ procurement, transplant preservation and improved immunosuppression medication. Despite the approximately 10% lower survival probability by 10-year follow-up with older donor kidneys, one must remain aware of the benefits of transplantation over dialysis, including improved recipient quality of life and a lower long-term financial burden.

It should be noted that the 10-year transplant outcomes presented in this study are inevitably, a consequence of donations which occurred approximately 10–15 years ago. Short-term transplant outcomes from older deceased donors have improved in the last few years [6, 24]. It is therefore also likely that the 10-year transplant outcomes in a recipient of an older deceased donor kidney transplanted today will be better than what we present in this article.

The restricted mean survival time provides an alternative way with which to present time to an event/survival data. One of the benefits of this method is that the result, often expressed in terms of years gained or lost in comparison with an alternative treatment, is easily interpretable for physicians and patients alike. Within the kidney transplant literature, we identified one other study using this method to examine kidney allograft survival in older deceased donor kidneys [5]. Lim *et al.* presented mean functioning graft years restricted to 16-year follow-up of 7.1 years for old recipients (≥55 years) of old donor kidneys (≥55 years) [5]. In other words for sixteen-year follow-up, the mean functioning graft survival time was 7 years, whereas the mean functioning graft years in our study were between 7 and 7.5 years within a shorter follow-up of 10 years. The cohort used in the study by Lim *et al.* was transplanted between 1991 and 2006, and therefore, the inclusion of transplant outcomes from the 1990s is the likely explanation for the poorer outcomes seen in their study.

This study was not designed to compare survival outcomes of young recipients receiving either young donor kidneys or old donor kidneys. It is well documented that survival outcomes are better for younger recipients if they receive younger donor's kidneys [25]. Furthermore, younger patients are likely to undergo retransplantation; therefore, it is recommended that they should not receive older donor kidneys given the shorter graft survival time and associated risk of

sensitization [6]. Nevertheless, as shown in this study, kidney transplantations from older donors into younger recipients do take place, as such, it is important to quantify the survival outcomes of these allografts.

This study is subject to the traditional limitations associated with observational studies, in particular the inability to control for other potential confounding factors. We lacked information on other donor factors which contribute to the risk of graft loss such as donor history of diabetes and cause of death. However, by performing a paired analysis, a kidney from the same older deceased donor was present in the young recipient and the older recipient group. We thereby attempted to eliminate any donor-associated factors which may have resulted in bias. However, one cannot be completely sure that even though the donor was the same, the kidneys were identical, for example there may have been disparities in kidney size or the presence of cysts between the two kidneys. Although both groups of paired older recipients, that is those paired to the younger recipients in group 1 or group 2 had the same median age, there were differences between the groups; of those paired to the group 1 younger recipients (with a median age of 52 years), only 3% had a preemptive transplant, compared to 9% of the older recipients paired to the group 2 younger recipients (with a median age of 41). Moreover, the graft survival at 10-year follow-up was lower in the older recipients paired with the group 1 younger recipients compared with the older recipients paired to the group 2 younger recipients (40% vs 49%, respectively). This may imply that clinicians selectively allocate the 'better quality' older deceased donor kidneys to the younger recipients and to the healthier older recipients. Therefore, the study design employed by this study to overcome the limited donor details available to us may have introduced a selection bias into the study. As such, these results cannot be considered generalizable to all donor kidneys from deceased donors aged between 55 and 70 years. We did not have access to transplant factors known to influence allograft outcomes such as the method of graft preservation, panel reactive antibodies and immunosuppression data, or information detailing episodes of delayed graft function or acute rejection therefore we do not know how many episodes each group experienced or the impact of these events. Nor do we have an accurate record of the causes of graft loss. Despite these limitations, there are a number of strengths in this study including the paired donor design, the relatively large cohort of recipients from a nine European countries/regions and the reasonably long follow-up time. Furthermore, the novel restricted mean survival time method used in this study provides easily interpretable estimates of the number of years gained or lost or the percentage reduction of expected restricted mean survival time.

Conclusion

The aim of this study was to quantify how long kidney allografts from older deceased donors are expected to function for whilst considering the donor–recipient age difference. In line with kidney transplant outcomes overall, 10-year graft survival probabilities from older deceased donors have improved, though they remain approximately 10% lower than the European average kidney transplant survival probabilities. Compared to the older recipients, the mean number of functioning graft years at 10 years was 6 months longer in the younger recipients. Older deceased donor kidneys remain a useful transplant resource, particularly for similar-aged recipients.

Authorship

MP: designed the study, prepared the data, wrote the statistical analysis plan, performed the analysis, interpreted the results and drafted and revised the manuscript. She is the guarantor. KJJ: designed the study, cowrote the statistical analysis plan, interpreted the results and revised the manuscript. FC: interpreted the results and revised the manuscript. AC, HE, PF and JH: contributed the data, interpreted the results and revised the manuscript. GH: contributed to the statistical analysis plan, interpreted the results and revised the manuscript. AH: contributed the data, interpreted the results and revised the manuscript. RK, ML, AM, KM, JP, KGP, SSS and JPT: contributed the data, interpreted the results and revised the manuscript. ZAM: interpreted the results and revised the manuscript. RR: designed the study, interpreted the results and revised the manuscript. VSS: designed the study, cowrote the statistical analysis plan, interpreted the results and revised the manuscript.

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Conflict of interest

The authors have declared no conflicts of interest.

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REFERENCES

1. Wu DA, Watson CJ, Bradley JA, Johnson RJ, Forsythe JL, Oniscu GC. Global trends and challenges in deceased donor kidney allocation. *Kidney Int* 2017; **91**: 1287.
2. Kidney Transplantation: Deceased Donor Organ Allocation. http://wwwodtnhsuk/pdf/kidney_allocation_policypdf 4, last accessed 23.09.2015.
3. Akoh JA, Rana TA. Impact of donor age on outcome of kidney transplantation from controlled donation after cardiac death. *Saudi J Kidney Dis Transpl* 2013; **24**: 673.
4. Keith DS, Dematteos A, Golconda M, Prather J, Norman D. Effect of donor recipient age match on survival after first deceased donor renal transplantation. *J Am Soc Nephrol* 2004; **15**: 1086.
5. Lim WH, Chang S, Chadban S, *et al.* Donor-recipient age matching improves years of graft function in deceased-donor kidney transplantation. *Nephrol Dial Transplant* 2010; **25**: 3082.
6. Pascual J, Zamora J, Pirsch JD. A systematic review of kidney transplantation from expanded criteria donors. *Am J Kidney Dis* 2008; **52**: 553.
7. Oppenheimer F, Aljama P, Asensio Peinado C, Bustamante Bustamante J, Crespo Albiach JF, Guirado Perich L. The impact of donor age on the results of renal transplantation. *Nephrol Dial Transplant* 2004; **19**(Suppl 3): iii11.
8. de Fijter JW. Counselling the elderly between hope and reality. *Nephrol Dial Transplant* 2011; **26**: 2079.
9. Eurotransplant. Annual report 2015. https://wwweurotransplantorg/cms/media objectphp?file=AR_ET_20153pdf. Accessed 22nd June 2016.
10. Scandiatransplant. Annual Report 2014. http://wwwscandiatransplantorg/resources/AnnualScandiatransplantdata report2014pdf. 2015.
11. Pippias M, Jager KJ, Kramer A, *et al.* The changing trends and outcomes in renal replacement therapy: data from the ERA-EDTA Registry. *Nephrol Dial Transplant* 2015; **31**: 831.
12. Zhang X. Comparison of restricted mean survival times between treatments based on a stratified Cox model. *Bio-Algorithms Med-Syst* 2013; **9**: 183.
13. Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. *Comput Methods Programs Biomed* 1997; **54**: 201.
14. Royston P, Parmar MK. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Methodol* 2013; **13**: 152.
15. Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? *Nephrol Dial Transplant* 2013; **28**: 2670.
16. Transplantation EEGoR. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.13 Analysis of patient and graft survival. *Nephrol Dial Transplant* 2002; **17**(Suppl 4): 60.
17. Couchoud C, Dantony E, Elsensohn MH, *et al.* Restricted mean survival time over 15 years for patients starting renal replacement therapy. *Nephrol Dial Transplant* 2017; **2**: ii60.
18. Waiser J, Schreiber M, Budde K, *et al.* Age-matching in renal transplantation. *Nephrol Dial Transplant* 2000; **15**: 696.
19. de Fijter JW. The impact of age on rejection in kidney transplantation. *Drugs Aging* 2005; **22**: 433.
20. Curschellas E, Landmann J, Durig M, *et al.* Morphologic findings in "zero-hour" biopsies of renal transplants. *Clin Nephrol* 1991; **36**: 215.
21. Melk A, Schmidt BM, Braun H, *et al.* Effects of donor age and cell senescence on kidney allograft survival. *Am J Transplant* 2009; **9**: 114.
22. Woo YM, Gill JS, Johnson N, Pereira BJ, Hariharan S. The advanced age deceased kidney donor: current

outcomes and future opportunities. *Kidney Int* 2005; **67**: 2407.
23. Tullius SG, Tran H, Guleria I, Malek SK, Tilney NL, Milford E. The combination of donor and recipient age is critical in determining host immunoresponsiveness and renal transplant outcome. *Ann Surg* 2010; **252**: 662.
24. Martinez-Vaquera S, Navarro Cabello MD, Lopez-Andreu M, *et al.* Outcomes in renal transplantation with expanded-criteria donors. *Transpl Proc* 2013; **45**: 3595.
25. Ma MK, Lim WH, Craig JC, Russ GR, Chapman JR, Wong G. Mortality among younger and older recipients of kidney transplants from expanded criteria donors compared with standard criteria donors. *Clin J Am Soc Nephrol* 2016; **11**: 128.